

=> s paroxetine(l) (formi? or formy? or forma?)

2997 PAROXETINE

679681 FORMI?

71422 FORMY?

3069874 FORMA?

L4 105 PAROXETINE(L) (FORMI? OR FORMY? OR FORMA?)

=> s l4 and (puri? or pur?)

1022494 PURI?

1823011 PUR?

L5 8 L4 AND (PURI? OR PUR?)

=> d bib hit 1-8

L5 ANSWER 1 OF 8 CAPLUS COPYRIGHT 2007 ACS on STN

AN 2006:1083758 CAPLUS

DN 146:33238

TI An HPLC method for the indirect quantification of a quinone adduct of the drug paroxetine

AU Zukowski, Janusz; Bryant, Duncan; Camilleri, Patrick

CS Analytical Chemistry, GlaxoSmithKline, Tonbridge, Kent, UK

SO Acta Poloniae Pharmaceutica (2006), 63(3), 175-180

CODEN: APPHAX; ISSN: 0001-6837

PB Polish Pharmaceutical Society

DT Journal

LA English

RE.CNT 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD

ALL CITATIONS AVAILABLE IN THE RE FORMAT

AB An HPLC method was developed for the quantification of low levels of a catechol derivative and a quinone adduct of paroxetine in the presence of excess drug substance. Due to its inherent instability, the paroxetine quinone adduct is not available as a pure compound so that an indirect method was developed for its quantification. This procedure is based on the assumption that one mol. of the catechol (or more precisely the corresponding 1,2-benzoquinone) reacts with one mol. of paroxetine to produce one mol. of paroxetine quinone adduct. In the presence of paroxetine excess, pseudo-first-order kinetics was used to study the formation of the unstable product. A detector response factor for the paroxetine quinone adduct was calculated as a function of the response factor for the paroxetine catechol derivative, after considering a mass balance of the reaction. Using the methodol. outlined, quant. anal. was carried out of the paroxetine catechol derivative and the paroxetine quinone adduct in batches of paroxetine drug substance.

L5 ANSWER 2 OF 8 CAPLUS COPYRIGHT 2007 ACS on STN

AN 2004:41440 CAPLUS

DN 140:93934

TI Process for producing piperidine compounds, specifically trans-4-(4-fluorophenyl)-3-(hydroxymethyl)piperidine and derivatives, useful as intermediates for paroxetine

IN Lim, Kwang-Min

PA CLS Laboratories, Inc., S. Korea

SO PCT Int. Appl., 15 pp.

CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2004005254	A1	20040115	WO 2003-KR1327	20030704
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,				

CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,  
 GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KZ, LC, LK, LR, LS,  
 LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG,  
 PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR,  
 TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW  
 RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY,  
 KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES,  
 FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR,  
 BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

KR 2004004745 A 20040114 KR 2002-39088 20020705  
 AU 2003245102 A1 20040123 AU 2003-245102 20030704

PRAI KR 2002-39088 A 20020705  
 WO 2003-KR1327 W 20030704

OS CASREACT 140:93934; MARPAT 140:93934

RE.CNT 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD

ALL CITATIONS AVAILABLE IN THE RE FORMAT

AB The invention relates to a new process for preparing pharmaceutical intermediate compds. of formula I [R1 = H, straight or branched C1-10 alkyl with or without substituent(s), straight or branched C1-10 alkoxy with or without substituent(s), aryl with or without substituent(s), formyl or alkylcarbonyl]. I are intermediates for a well-known antidepressant and selective serotonin reuptake inhibitor, paroxetine. Using the invention process, I can be prepared simply, with a high product yield and a high purity of 99% or more, without using any dangerous processes. The overall process involves (1) cyclization of an acyclic amine II [Y = leaving group, particularly Cl, Br, iodo, MeSO2O, p-MeC6H4SO2O; R1 as above; R2 = alkoxycarbonyl, arylalkoxycarbonyl, aryloxycarbonyl or cyano] and isomerization of the product, using a base, and (2) reduction of the resultant trans-isomeric piperidine compound III with a reducing agent to obtain I. For instance, treatment of II [Y = Cl, R1 = Me, R2 = CO2Me] in THF with LiN(SiMe3)2 in hexane at -10° and stirring to completion gave III [R1 = Me, R2 = CO2Me] in 95.1% yield and 98.5% purity. Reduction of the latter ester with LiAlH4 in THF at 10° gave I [R1 = Me] in 78.4% yield and 99.3% purity.

IT 109887-53-8P, trans-N-Methyl-4-(4-fluorophenyl)-3-(hydroxymethyl)piperidine 188869-26-3DP, trans-4-(4-Fluorophenyl)-3-(hydroxymethyl)piperidine, derivs. 188869-26-3P, trans-4-(4-Fluorophenyl)-3-(hydroxymethyl)piperidine 644468-14-4P, trans-N-Formyl-4-(4-fluorophenyl)-3-(hydroxymethyl)piperidine  
 RL: IMF (Industrial manufacture); SPN (Synthetic preparation); PREP (Preparation)  
 (target intermediate; improved preparation of trans-(fluorophenyl)(hydroxymethyl)piperidine derivs. useful as paroxetine intermediates)

L5 ANSWER 3 OF 8 CAPLUS COPYRIGHT 2007 ACS on STN

AN 2003:417743 CAPLUS

DN 139:12268

TI Preparation and compositions of N-formylparoxetine derivatives

IN Hoorn, Hans Jan; Peters, Theodorus Hendricus Antonius; Picha, Frantisek

PA Synthon B.V., Neth.

SO PCT Int. Appl., 39 pp.

CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003044012	A1	20030530	WO 2002-NL654	20021015
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH,				

PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ,  
 UA, UG, US, UZ, VN, YU, ZA, ZM, ZW  
 RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY,  
 KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES,  
 FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF,  
 CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

CA 2464327	A1	20030530	CA 2002-2464327	20021015
AU 2002330771	A1	20030610	AU 2002-330771	20021015
EP 1440067	A1	20040728	EP 2002-768169	20021015
EP 1440067	B1	20041222		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK				
DE 20220955	U1	20041007	DE 2002-20220955	20021015
HU 200401895	A2	20041228	HU 2004-1895	20021015
AT 285408	T	20050115	AT 2002-768169	20021015
NZ 532432	A	20050225	NZ 2002-532432	20021015
PT 1440067	T	20050228	PT 2002-768169	20021015
ES 2230516	T3	20050501	ES 2002-2768169	20021015
US 2003125560	A1	20030703	US 2002-274051	20021021
US 6703408	B2	20040309		
US 2004147497	A1	20040729	US 2004-759437	20040120
US 2004266825	A1	20041230	US 2004-759436	20040120
NO 2004002101	A	20040521	NO 2004-2101	20040521
PRAI US 2001-330430P	P	20011022		
WO 2002-NL654	W	20021015		
US 2002-274051	A3	20021021		

RE.CNT 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD  
 ALL CITATIONS AVAILABLE IN THE RE FORMAT

AB The invention relates to a compound or composition comprising N-formylparoxetine I and 0 to 99.97% of a paroxetine selective serotonin reuptake inhibitor, comprising an effective amount of a paroxetine agent and at least one pharmaceutically acceptable excipient. The invention also relates to a process for producing a paroxetine compound which comprises treating an N-formylparoxetine compound I with a deformylation agent. A third aspect of the invention relates to a process for determining the stability or purity of a paroxetine substance or composition, which comprises assaying a paroxetine substance or composition for the presence of an N-formylparoxetine compound I, which is an impurity. For example, (3S,4R)-4-(4-fluorophenyl)piperidine-3-methanol was formylated to give N-formylparoxol (100%). Tosylation of the alc., followed by substitution with sesamol gave (3S,4R)-I, which was deformylated using MeSO<sub>3</sub>H to afford paroxetine•MeSO<sub>3</sub>H (46%).

ST formyl paroxetine prepn compn impurity

IT Stability

(of paroxetine substance or composition; preparation and compns. of N-formyl derivs. of paroxetine)

IT 5-HT reuptake inhibitors

Drug delivery systems

(preparation and compns. of N-formyl derivs. of paroxetine)

IT 533935-67-0P, N-Formylparoxetine 533935-68-1P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(composition impurity; preparation and compns. of N-formyl derivs. of paroxetine)

IT 7757-93-9

RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(excipient; preparation and compns. of N-formyl derivs. of paroxetine)

IT 533935-65-8P, N-Formylparoxol 533935-66-9P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(intermediate; preparation and compns. of N-formyl derivs. of paroxetine)

IT 98-59-9, Tosyl chloride 533-31-3, Sesamol 125224-43-3,  
(3S,4R)-4-(4-Fluorophenyl)piperidine-3-methanol  
RL: RCT (Reactant); RACT (Reactant or reagent)  
(preparation and compns. of N-formyl derivs. of paroxetine)

IT 61869-08-7, Paroxetine  
RL: RCT (Reactant); THU (Therapeutic use); BIOL (Biological study); RACT  
(Reactant or reagent); USES (Uses)  
(preparation and compns. of N-formyl derivs. of paroxetine)

IT 78246-49-8P, Paroxetine hydrochloride 217797-14-3P,  
Paroxetine methanesulfonate  
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological  
study); PREP (Preparation); USES (Uses)  
(preparation and compns. of N-formyl derivs. of paroxetine)

IT 64006-44-6, Paroxetine maleate 72471-80-8, Paroxetine  
acetate  
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
(preparation and compns. of N-formyl derivs. of paroxetine)

L5 ANSWER 4 OF 8 CAPLUS COPYRIGHT 2007 ACS on STN  
AN 2002:977660 CAPLUS  
DN 138:29184  
TI A process for preparing paroxetine hydrochloride limiting  
formation of pink compounds  
IN Avrutov, Ilya; Pilarski, Gideon  
PA Teva Pharmaceutical Industries Ltd., Israel; Teva Pharmaceuticals USA,  
Inc.  
SO PCT Int. Appl., 25 pp.  
CODEN: PIXXD2  
DT Patent  
LA English  
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2002102382	A1	20021227	WO 2002-US19016	20020614
	WO 2002102382	A9	20030306		
	W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW			
	RW:	GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG			
	CA 2447808	A1	20021227	CA 2002-2447808	20020614
	US 2003083501	A1	20030501	US 2002-172521	20020614
	EP 1406625	A1	20040414	EP 2002-752054	20020614
	R:	AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR			
	CN 1516585	A	20040728	CN 2002-811890	20020614
	HU 200400216	A2	20040728	HU 2004-216	20020614
	TR 200302081	T2	20040921	TR 2003-2081	20020614
	JP 2005501819	T	20050120	JP 2003-504969	20020614
	ZA 2003009049	A	20041121	ZA 2003-9049	20031120
PRAI	US 2001-298603P	P	20010614		
	US 2001-326993P	P	20011005		
	US 2002-346048P	P	20020104		
	WO 2002-US19016	W	20020614		

RE.CNT 9        THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD  
                 ALL CITATIONS AVAILABLE IN THE RE FORMAT

TI    A process for preparing paroxetine hydrochloride limiting  
      formation of pink compounds  
ST    paroxetine hydrochloride purity prepn; buffer paroxetine  
      hydrochloride purity prepn  
IT    Mental and behavioral disorders  
      (depression; preparation of paroxetine hydrochloride limiting  
      formation of pink compds.)  
IT    Mental and behavioral disorders  
      (obsession-compulsion; preparation of paroxetine hydrochloride  
      limiting formation of pink compds.)  
IT    Anxiety  
      (panic disorder; preparation of paroxetine hydrochloride limiting  
      formation of pink compds.)  
IT    Mental and behavioral disorders  
      (post-traumatic stress disorder; preparation of paroxetine  
      hydrochloride limiting formation of pink compds.)  
IT    Ovarian cycle  
      (premenstrual syndrome; preparation of paroxetine hydrochloride  
      limiting formation of pink compds.)  
IT    Antioxidants  
      Anxiety  
      Buffers  
      Parkinson's disease  
      Recrystallization  
      (preparation of paroxetine hydrochloride limiting  
      formation of pink compds.)  
IT    7440-44-0, Carbon, uses  
      RL: MOA (Modifier or additive use); USES (Uses)  
      (activated; preparation of paroxetine hydrochloride limiting  
      formation of pink compds.)  
IT    50-81-7, Ascorbic acid, uses    128-37-0, BHT, uses    25013-16-5, BHA  
      RL: MOA (Modifier or additive use); USES (Uses)  
      (antioxidant; preparation of paroxetine hydrochloride limiting  
      formation of pink compds.)  
IT    12125-02-9, Ammonium chloride, uses  
      RL: MOA (Modifier or additive use); USES (Uses)  
      (preparation of paroxetine hydrochloride limiting  
      formation of pink compds.)  
IT    67-56-1, Methanol, uses    67-64-1, Acetone, uses  
      RL: NUU (Other use, unclassified); PEP (Physical, engineering or chemical  
      process); PYP (Physical process); PROC (Process); USES (Uses)  
      (preparation of paroxetine hydrochloride limiting  
      formation of pink compds.)  
IT    61869-08-7, Paroxetine  
      RL: RCT (Reactant); RACT (Reactant or reagent)  
      (preparation of paroxetine hydrochloride limiting  
      formation of pink compds.)  
IT    78246-49-8P, Paroxetine hydrochloride    110429-35-1P,  
      Paroxetine hydrochloride hemihydrate  
      RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological  
      study); PREP (Preparation); USES (Uses)  
      (preparation of paroxetine hydrochloride limiting  
      formation of pink compds.)

L5    ANSWER 5 OF 8    CAPLUS    COPYRIGHT 2007 ACS on STN

AN    2002:832615    CAPLUS

DN    137:329533

TI    Optimized procedures for the manufacture of paroxetine salts

IN    Upadhyaya, Subhash P.; Ronsen, Bruce

PA    Pentech Pharmaceuticals, Inc., USA

SO    PCT Int. Appl., 55 pp.

CODEN: PIXXD2

DT Patent  
LA English  
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2002085360	A1	20021031	WO 2002-US13378	20020425
	W:			AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM	
	RW:			GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG	
	US 2003032809	A1	20030213	US 2002-133726	20020425
PRAI	US 2001-286590P	P	20010425		
	US 2001-290411P	P	20010511		
	US 2001-295471P	P	20010601		
	US 2001-333530P	P	20011120		

RE.CNT 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

AB Methods for manufacturing amorphous paroxetine hydrochloride by mixing a carboxylic acid salt of paroxetine with hydrogen chloride and isolating the amorphous paroxetine hydrochloride are described. Also described herein are methods for manufacturing substantially pure paroxetine free base and methods for obtaining paroxetine salts with carboxylic acids, such as paroxetine acetate, paroxetine trifluoroacetate, and paroxetine formate, or with mineral acids, such as paroxetine carbonate, paroxetine phosphate, paroxetine sulfate, and analogous salts thereof. The paroxetine salts may be formulated for the use in treatment of medical disorders.

IT 72471-80-8P, Paroxetine acetate 236391-41-6P, Paroxetine propionate 236391-42-7P, Paroxetine formate 473829-66-2P 473829-67-3P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)  
(optimized procedures for manufacture of paroxetine salts for dosage forms)

L5 ANSWER 6 OF 8 CAPLUS COPYRIGHT 2007 ACS on STN  
AN 2000:911247 CAPLUS  
DN 134:61560  
TI Process for the production of paroxetine hydrochloride  
IN Jones, David Alan  
PA Smithkline Beecham P.L.C., UK  
SO PCT Int. Appl., 14 pp.  
CODEN: PIXXD2

DT Patent  
LA English  
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2000078752	A1	20001228	WO 2000-GB2425	20000622
	W:			AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM	
	RW:			GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ,	

CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRAI GB 1999-14585 A 19990622

RE.CNT 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD

ALL CITATIONS AVAILABLE IN THE RE FORMAT

AB Paroxetine-HCl is prepared by a process in which a suspension of paroxetine maleate is treated with an excess of HCl to form a solution containing paroxetine, maleic acid, and HCl, and crystallizing substantially pure paroxetine-HCl from the solution. In this process paroxetine maleate in solution is directly converted to solid paroxetine hydrochloride, avoiding formation of paroxetine free base and subsequent re-acidifying with hydrogen chloride. The process surprisingly results in good yield and purity without the complication of large amts. of maleic acid contamination, and so is suitable for large-scale manufacture

IT 110-16-7, Maleic acid, formation (nonpreparative)

RL: FMU (Formation, unclassified); FORM (Formation, nonpreparative)  
(process for the production of paroxetine hydrochloride)

L5 ANSWER 7 OF 8 CAPLUS COPYRIGHT 2007 ACS on STN

AN 1999:227255 CAPLUS

DN 131:67604

TI O- and N-demethylation of venlafaxine in vitro by human liver microsomes and by microsomes from cDNA-transfected cells; effect of metabolic inhibitors and SSRI antidepressants

AU Fogelman, Steven M.; Schmider, Jurgen; Venkatakrisnan, Karthik; Von Moltke, Lisa L.; Harmatz, Jerold S.; Shader, Richard I.; Greenblatt, David J.

CS Department of Pharmacology and Experimental Therapeutics, Tufts University School of Medicine, Boston, MA, 02111, USA

SO Neuropsychopharmacology (1999), 20(5), 480-490  
CODEN: NEROEW; ISSN: 0893-133X

PB Elsevier Science Inc.

DT Journal

LA English

RE.CNT 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD

ALL CITATIONS AVAILABLE IN THE RE FORMAT

AB The biotransformation of venlafaxine (VF) into its two major metabolites, O-desmethylvenlafaxine (ODV) and N-desmethylvenlafaxine (NDV) was studied in vitro with human liver microsomes and with microsomes containing individual human cytochromes from cDNA-transfected human lymphoblastoid cells. VF was coincubated with selective cytochrome P 450 (CYP) inhibitors and several selective serotonin reuptake inhibitors (SSRIs) to assess their inhibitory effect on VF metabolism. Formation rates for ODV incubated with human microsomes were consistent with Michaelis-Menten kinetics for a single-enzyme mediated reaction with substrate inhibition. Mean parameters determined by non-linear regression were:  $V_{max} = 0.36$  nmol/min/mg protein,  $K_m = 41 \mu M$ , and  $K_s 22901 \mu M$  ( $K_s$  represents a constant which reflects the degree of substrate inhibition). Quinidine (QUI) was a potent inhibitor of ODV formation with a  $K_i$  of  $0.04 \mu M$ , and paroxetine (PX) was the most potent SSRI at inhibiting ODV formation with a mean  $K_i$  value of  $0.17 \mu M$ . Studies using expressed cytochromes showed that ODV was formed by CYP2C9, -2C19, and -2D6. CYP2D6 was dominant with the lowest  $K_m$ ,  $23.2 \mu M$ , and highest intrinsic clearance ( $V_{max}/K_m$  ratio). No unique model was applicable to the formation of NDV for all four livers tested. Parameters determined by applying a single-enzyme model were  $V_{max} = 2.14$  nmol/min/mg protein, and  $K_m = 2504 \mu M$ . Ketoconazole was a potent inhibitor of NDV production, although its inhibitory activity was not as great as observed with pure 3A substrates. NDV formation was also reduced by 42% by a polyclonal rabbit antibody against rat liver CYP3A1. Studies using expressed cytochromes showed that NDV was formed by CYP2C9, -2C19, and -3A4. The highest intrinsic clearance was attributable to CYP2C19 and the lowest to CYP3A4. However the high in vivo abundance of 3A isoforms will magnify the importance of this cytochrome.

Fluvoxamine (FX), at a concentration of 20  $\mu$ M, decreased NDV production by 46% consistent with the capacity of FX to inhibit CYP3A, 2C9, and 2C19. These results are consistent with previous studies that show CYP2D6 and -3A4 play important roles in the formation of ODV and NDV, resp. In addition the authors have shown that several other CYPs have important roles in the biotransformation of VF.

L5 ANSWER 8 OF 8 CAPLUS COPYRIGHT 2007 ACS on STN

AN 1992:17824 CAPLUS

DN 116:17824

TI Radiosynthesis and evaluation of N-(3-[18F]fluoropropyl)paroxetine as a radiotracer for in vivo labeling of serotonin uptake sites by PET

AU Suehiro, Makiko; Wilson, Alan A.; Scheffel, Ursula; Dannals, Robert F.; Ravert, Hayden T.; Wagner, Henry N., Jr.

CS Div. Nucl. Med., Johns Hopkins Med. Inst., Baltimore, MD, 21205-2179, USA

SO Nuclear Medicine and Biology (1991), 18(7), 791-6

CODEN: NMBIEO; ISSN: 0883-2897

DT Journal

LA English

AB To visualize serotonin uptake sites by positron emission tomog. (PET), N-(3-[18F]fluoropropyl)paroxetine ([18F]FPP) (I), a derivative of the selective serotonin uptake blocker paroxetine, was synthesized from 3-[18F]fluoropropyltosylate and paroxetine via a 1-pot procedure. The rate of formation of [18F]FPP was a function of the ratio of the initial amount of paroxetine to that of 1,3-propanediol bistosylate with which [18F]fluoropropyltosylate was synthesized. When the reaction mixture contained an excess amount of paroxetine over that of the propyl-bistosylate, the radiosynthesis followed by HPLC purifn., which took .apprx.90 min, gave [18F]FPP in a radiochem. yield of .apprx.8%, and in high radiochem. and chemical purity. The specific activity was  $2640 \pm 360$  mCi/ $\mu$ mol. The brain biodistribution of [18F]FPP showed no distinguishable localization in regions with high d. of serotonin uptake sites such as hypothalamus or olfactory tubercles. In vitro binding assays revealed that N-fluoropropylation of paroxetine reduced the affinity for the serotonin uptake site by 3 orders of magnitude.